Remarks

I. Status of the Claims

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 42-60 are pending in the application, with claims 42 and 52 being the independent claims. Claims 42 and 52 are sought to be amended. Support for the amendment to claim 42 can be found at, *e.g.*, page 7, lines 20-21. Support for the amendments to claim 52 can be found at, *e.g.*, page 6, lines 26-28, page 7, lines 3-4 and 20-21, and page 13, lines 6-8. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

II. Summary of the Office Action

In the Office Action dated August 6, 2008, the Examiner has withdrawn the rejections under 35 U.S.C. § 102(a) and (e) over Baker *et al.* (U.S. Pat. No. 7,029,874) and the rejection under 35 U.S.C. § 112, first paragraph. The Examiner has maintained the rejection under 35 U.S.C. § 102(b) over Eisenbach-Schwartz et al. (U.S. Pub. No. 2002/0072493) and has added an objection and two new rejections under 35 U.S.C. §§ 112, second paragraph, and 103(a).

III. Objection to Claims

In section 11 of the Office Action at page 6, claims 42 and 52 were objected to for minor informalities. The Examiner has suggested that the term "LRRCT domain" might be confusing. Office Action at page 6. Applicants respectfully disagree. However, in an effort to facilitate prosecution, and not in acquiescence to the Examiner's objection, Applicants have amended claims 42 and 52 to specify that LRRCT is an abbreviation for "leucine-rich-repeat domain C-terminal of the eight leucine-rich repeats," as clearly described in the specification at page 7, lines 20-21. Reconsideration and withdrawal of this objection is respectfully requested.

IV. Rejection Under 35 U.S.C. § 112, Second Paragraph, is Traversed

In section 12 of the Office Action at pages 6-7, claims 42-47, 49-56, and 58-60 were rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. In particular, the Examiner asserts that the phrase "eight leucine-rich repeats" as used in claims 42 and 52 is unclear. Applicants respectfully disagree and traverse this rejection.

Applicants submit that claims 42 and 52 are not indefinite and would be clearly understood by a person skilled in the art. The Examiner, however, contends that the phrase eight leucine-rich repeats is indefinite because "the specification does not describe what 8 LRRs are and where these are located." Office Action at page 7. The Examiner asserts that it is unclear if eight leucine-rich repeats means "a sequence of 'LLLLLLLL'" or that "8 leucine residues would encompass 1 leucine-rich region." *Id.* at pages 6-7. In reference to SEQ ID NO:3, the Examiner further states that "it is unclear where the 8

leucine-rich repeats would be located in the sequence, since there are leucine residues throughout the protein sequence." *Id.* at page 7.

Applicants respectfully assert that the Examiner's focus on the definiteness of eight leucine-rich repeats is misplaced, and that the proper inquiry under 35 U.S.C. § 112, second paragraph, is consideration of "the claim as a whole to determine whether the claim apprises *one of ordinary skill in the art* of its scope." M.P.E.P. § 2173.02 (emphasis added). M.P.E.P. § 2173.02 states:

> The essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a *reasonable* degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of:
> (A) The content of the particular application disclosure;
> (B) The teachings of the prior art; and
> (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

Id. (emphasis added). In view of this framework, Applicants assert that claims 42 and 52 set out and circumscribe the subject matter claimed therein with a reasonable degree of clarity and particularity.

Claims 42 and 52 require that the soluble Nogo receptor-1 polypeptide comprises an NT domain, eight leucine-rich repeats, and an LRRCT domain. As the Examiner points out, the specification discloses that "[f]ull-length Nogo receptor-1 consists of a signal sequence, a N-terminus region (NT), eight leucine-rich repeats (LRR), a LRRCT region (a leucine-rich-repeat domain C-terminal of the eight leucine-rich repeats), a C-terminus region (CT) and a GPI anchor." Specification at page 7, lines 19-22. The specification also discloses the polypeptide sequences of, *e.g.*, human and rat Nogo receptor-1. *See id.* at Table 1. Thus, the specification discloses the polypeptide

sequences of human and rat Nogo receptor-1, that full-length Nogo receptor-1 has eight leucine-rich repeats, and that C-terminal to those eight leucine-rich repeats, there is an additional leucine-rich repeat domain.

In addition, two references available at the time of the invention, PCT/US02/32007 and PCT/US03/25004, which were incorporated by reference in their entireties in the present specification, describe additional soluble Nogo receptor-1 polypeptides that may be used in the methods of the invention. *See* specification at page 8, lines 9-11. These international applications also provide amino acid sequences and schematic representations of the domains of a Nogo receptor and show representative examples of the eight leucine-rich repeats present in Nogo receptor polypeptides. *See e.g.*, PCT/US02/32007 at pages 24-25 and Table 1, and PCT/US03/25004, Figure 1. Moreover, as further evidence of the teachings of the prior art at the time of the invention, Kobe, B., and Kajava, A.V., *Current Opinion in Structural Biology* 11:725-32 (2001) (attached hereto as Exhibit A), provides a detailed structure-function review of leucine-rich repeats, including how to identify leucine-rich repeat consensus sequences.[1] *See e.g.*, Kobe and Kajava at page 725.

Thus, when viewed with reference to the present specification and the teachings of the prior art, one of ordinary level of skill in the art at the time of the invention could readily ascertain the scope of the phrase "eight leucine-rich repeats" as used in claims 42

[1] Applicants respectfully point out that the "InterPro: IPR001611 Leucine-rich repeat" reference that the Examiner downloaded from the European Bioinformatics Institute website, www.ebi.ac.uk/interpro/IEntry?ac=IPR001611, also discusses the consensus sequence of leucine-rich repeats, which could be used by one of skill in the art to identify eight leucine-rich repeats in soluble Nogo receptor-1. *See* page 2 of 5.

and 52. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

V. Rejection over Eisenbach-Schwartz et al. Under 35 U.S.C. § 102(b) is Traversed

In section 5 of the Office Action at pages 3-6, claims 42-44, 52, and 53 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Eisenbach-Schwartz *et al.* (U.S. Pub. No. 2002/0072493) (hereinafter "Eisenbach-Schwartz"). Applicants would like to point out that in the previous Office Action (PTO Prosecution File Wrapper Paper No. 20071128), dated December 11, 2007, the Examiner rejected claims 1-3 over Eisenbach-Schwartz. In Applicants' Amendment and Reply Under 37 C.F.R. § 1.114, filed May 14, 2008, Applicants clarified that claims 1-3 were cancelled in advance of prosecution by a Preliminary Amendment and traversed the rejection with respect to claims 42-44 in case the Examiner had misquoted the pending claims. The Examiner has now applied the rejection over Eisenbach-Schwartz to presently pending claims 42-44, 52, and 53. Office Action at page 3. Applicants respectfully traverse this rejection.

Under 35 U.S.C. §102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). As presented, claims 42 and 52, and the claims depending therefrom, are drawn to a method for reducing the levels of Aβ peptide in a mammalian brain and a method of treating a disease, disorder, or condition associated with plaques of Aβ peptide in a mammalian brain, comprising administering a therapeutically effective amount of a soluble Nogo receptor-1 polypeptide, wherein said soluble Nogo receptor-1 polypeptide

comprises an NT domain, eight leucine-rich repeats, and an LRRCT domain. These methods are not disclosed by Eisenbach-Schwartz.

Eisenbach-Schwartz is broadly directed to methods for the promotion of nerve regeneration or to confer neuroprotection and prevent or inhibit neuronal degeneration within the nervous system ("NS") using activated T cells and NS-specific antigens. These methods cannot, either expressly or inherently, anticipate methods for reducing levels of Aβ peptide or treating a disease, disorder, or condition associated with plaques of Aβ peptide comprising administering a soluble Nogo receptor-1 polypeptide. Furthermore, although Eisenbach-Schwartz teaches peptides of NS-specific antigens, including Nogo receptor, the peptides disclosed in the reference, *see, e.g.*, page 9, paragraphs [0110-0112], do not encompass a *soluble* Nogo receptor-1 polypeptide that comprises an NT domain, eight leucine-rich repeats, and an LRRCT domain, as required by the present claims.

Despite Applicants' arguments, the Examiner appears to be reluctant to withdraw the rejection over Eisenbach-Schwartz because of the alleged indefiniteness of the phrase "eight leucine-rich repeats." Office Action at pages 5-6. As discussed above, based on the disclosure in the present specification and the teachings of the prior art, one of ordinary level of skill in the art at the time of the invention could readily ascertain the scope of the phrase "eight leucine-rich repeats" as used in claims 42 and 52. Thus, in view of the definiteness of eight leucine-rich repeats, Eisenbach-Schwartz does not disclose, either expressly or inherently, a soluble Nogo receptor-1 polypeptide that comprises an NT domain, eight leucine-rich repeats, and an LRRCT domain.

Therefore, Eisenbach-Schwartz does not disclose every element in the claims as currently presented, because the reference does not disclose methods for reducing levels of Aβ peptide or treating a disease, disorder, or condition associated with plaques of Aβ peptide comprising administering a soluble Nogo receptor-1 polypeptide that comprises an NT domain, eight leucine-rich repeats, and an LRRCT domain. Accordingly, under *Kalman*, Eisenbach-Schwartz cannot and does not anticipate the claims as currently presented, because this reference fails to disclose each and every limitation recited in the present claims. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) is therefore respectfully requested.

VI. Rejection over Strittmatter (U.S. Pat. No. 7,119,165) in View of Strittmatter (J. Mol. Neurosci., 19:117-121 (2002)) Under 35 U.S.C. § 103(a) is Traversed

In section 14 of the Office Action at pages 8-12, claims 42-45, 47, 51-53, and 60 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Strittmatter (U.S. Pat. No. 7,119,165) ("the '165 patent") in view of Strittmatter (J. Mol. Neurosci., 19:117-121 (2002)) ("Strittmatter"). Applicants respectfully disagree. However, in an effort to facilitate prosecution, and not in acquiescence to the Examiner's rejection, claim 52 has been amended to recite:

> A method of treating a disease, disorder or condition associated with plaques of Aβ peptide in a mammalian brain, comprising administering a therapeutically effective amount of a soluble Nogo receptor-1 polypeptide, wherein said soluble Nogo receptor-1 polypeptide comprises an NT domain, eight leucine-rich repeats, and an LRRCT (leucine-rich-repeat domain C-terminal of the eight leucine-rich repeats) domain and wherein said polypeptide reduces plaque deposits.

Support for the amendments to claim 52 can be found at, for example, page 6, lines 26-28, page 7, lines 3-4 and 20-21, and page 13, lines 6-8 of the specification as filed.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki,* 745 F.2d 1468, 1471-73 (Fed. Cir. 1984). As set forth in *Graham v. John Deere Co. of Kansas City*, "[u]nder § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined." 383 U.S. 1, 17 (1966). This has been the standard for 40 years, and remains the law today. *See KSR Int'l. Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). If, after these criteria are considered, the evidence indicates that the claimed invention is obvious over the prior art, it may be said that a *prima facie* case of obviousness has been established.

In addition, the Examiner must show reasons, explicit or otherwise, that would compel one of ordinary skill in the art to combine the references in order to make and use the claimed invention. To determine whether there is "an apparent reason to combine" the known elements as an application claims,

> it will be necessary . . . to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art. . . . To facilitate review, this analysis should be made explicit.

Id. at 1740-41; *see also* Memorandum from the United States Patent and Trademark Office, "Supreme Court decision on *KSR Int'l. Co. v. Teleflex, Inc.*," (May 3, 2007) ("The Court did not totally reject the use of 'teaching, suggestion, motivation' as a factor in the obviousness analysis. . . . [I]n formulating a rejection . . . based upon a combination of

prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.").

Applicants assert that the Examiner has failed to establish a *prima facie* case of obviousness as discussed below. Applicants further assert that there is no apparent reason to combine the prior art references cited by the Examiner to arrive at the claimed invention.

Claims 42 and 52, and the claims depending therefrom, are directed to a method for reducing the levels of Aβ peptide in a mammalian brain and a method of treating a disease, disorder, or condition associated with plaques of Aβ peptide in a mammalian brain, comprising administering a therapeutically effective amount of a soluble Nogo receptor-1 polypeptide, wherein said soluble Nogo receptor-1 polypeptide comprises an NT domain, eight leucine-rich repeats, and an LRRCT domain. As discussed above, claim 52 further specifies that the polypeptide reduces plaque deposits. The '165 patent does not disclose, suggest, or otherwise contemplate these methods.

The '165 patent discloses polypeptides of Nogo receptor-1 wherein said polypeptides inhibit Nogo receptor-mediated neurite outgrowth inhibition. *See, e.g.*, the '165 patent at col. 3, lines 51-53, and col. 97, lines 42-45. In addition, the '165 patent teaches a "method of treating a central nervous system disease, disorder or injury, e.g., spinal cord injury." S*ee, e.g.*, *id.* at col. 4, lines 28-30. However, as the Examiner correctly points out, the '165 patent does not teach or suggest a method of reducing the levels of Aβ peptide in a mammalian brain, nor does the '165 patent teach or suggest a method of treating a disease, disorder, or condition associated with plaques of Aβ peptide in a mammalian brain, comprising administering a therapeutically effective amount of a

soluble Nogo receptor-1 polypeptide, wherein said polypeptide reduces plaque deposits. Moreover, there is nothing in the '165 patent to suggest a relationship between Nogo receptor and Aβ peptide, as the '165 patent is directed to, *inter alia*, the interaction between Nogo receptor and Nogo ligand, *e.g.*, for decreasing Nogo-dependent inhibition of axonal growth in CNS neurons. *See, e.g., id.* at col. 3, lines 45-53.

These deficiencies are not cured by the disclosure of Strittmatter. Strittmatter is directed to the physiologic role of Nogo *ligand* and Nogo receptor in the modulation of axonal growth. *See* Strittmatter, page 117, Abstract. While Strittmatter mentions the "generally accepted" pathology of Alzheimer's Disease (AD), "that neuronal loss is initiated by the accumulation of the β-amyloid (Aβ) peptide and that this results in cognitive dysfunction," Strittmatter contemplates the promotion of axonal growth as a therapeutic approach, not reducing Aβ peptide. *Id.* at page 117, left column. For example, Strittmatter states that "the identification of Nogo and NgR provides the opportunity for novel and rational therapeutics *to promote axonal growth* in the adult mammalian CNS. . . . Specifically, the goal is to develop *a method to block Nogo action* in vivo, and thereby allow functional axonal regeneration and plasticity." *Id.* at page 120, left column (emphases added). Promoting axonal growth and methods of blocking Nogo action using, *e.g.*, Nogo receptor or a fragment thereof, does not obviate the subject matter of claims 42 and 52, and the claims depending therefrom, directed to a method of reducing the levels of Aβ peptide and a method of treating a disease, disorder, or condition associated with plaques of Aβ peptide in a mammalian brain, by reducing plaque deposits.

The Examiner argues that one of ordinary skill would have been motivated to combine the teachings of the '165 patent and Strittmatter, with a reasonable expectation of success, because both of these references teach the promotion of axonal growth as a possible therapy for neurodegenerative diseases or disorder, using Nogo receptor. *See* Office Action, page 10. The Examiner continues by asserting that Strittmattter:

> indicates that in AD, it is generally accepted that neuronal loss is initiated by the accumulation of the β-amyloid peptide and that this results in cognitive dysfunction, one would necessarily expect to reduce the levels of Aβ peptide in the mammalian brain when the soluble NgR-1 polypeptide is administered to the mammalian patient population.

Id. at pages 10-11. As explained above, the Examiner's focus on axonal growth, which involves the Nogo *ligand* and Nogo receptor, is misplaced, as one of ordinary skill in the art would not have been motivated to administer a soluble Nogo receptor-1 polypeptide to reduce Aβ peptide levels or to treat a disease, disorder, or condition associated with plaques of Aβ peptide in a mammalian brain, by reducing plaque deposits, based on the disclosure of methods of promoting axonal growth, even as the latter may pertain to AD therapy.[2]

Furthermore, the Examiner's statement that "one would necessarily expect to reduce the levels of Aβ peptide" seems to indicate that the Examiner is basing her rejection of the present method claims on inherent obviousness. Applicants respectfully

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[2] This distinction is further delineated in Strittmatter, which states that:

> if successful therapies are developed to delay or halt neuronal death in AD, then means to promote increased axonal growth and new synaptic connections from remaining cells should provide a mechanism for *recovery of lost function* as opposed to simply halting the progression of disease. The recent excitement surrounding the hypothesis that selective secretase inhibitors might limit Aβ production and neuronal loss emphasizes the need to develop therapeutics to *improve axonal sprouting and regeneration.*

Strittmatter, page 117 (emphases added). Thus, Strittmatter clearly contemplates the use of Nogo receptor in promoting axonal growth but <u>not</u> to delay or halt neuronal death in AD, *e.g.*, by limiting Aβ peptide production.

wish to remind the Examiner, however, that there is no such thing as inherent obviousness, since inherency and obviousness are different legal concepts. *See In re Spormann*, 363 F.2d 444 (C.C.P.A. 1966); *In re Rijckaert*, 9 F.3d 1531 (Fed. Cir. 1993). That which is inherent cannot be obvious, since inherent information "is not necessarily known . . . . [and] [o]bviousness cannot be predicated on what is unknown." *Spormann*, 363 F.2d at 448. Because the present rejection is based on obviousness, any contention by the Examiner that is based on the possible presence of inherent knowledge in Strittmatter must necessarily fail. Moreover, one of ordinary skill in the art at the time of the invention would not have expected soluble Nogo receptor-1 polypeptide to reduce the levels of Aβ peptide because one of ordinary skill in the art would not have appreciated that Nogo receptor-1 interacted with Aβ peptide or its precursor protein, amyloid precursor protein (APP). As indicated in the present specification, Applicants were the first to elucidate and characterize this relationship. *See, e.g.*, the specification at page 17, line 10, through page 22, line 16 (Examples 1-6).

Therefore, Applicants submit that the combination of the '165 patent and Strittmatter does not disclose, suggest, or otherwise contemplate the presently claimed invention because neither reference provides any motivation, either explicit or implicit, to administer a soluble Nogo receptor-1 polypeptide in a method for reducing the levels of Aβ peptide in a mammalian brain or in a method for treating a disease, disorder, or condition associated with plaques of Aβ peptide in a mammalian brain, wherein the polypeptide reduces plaque deposits. Accordingly, a *prima facie* case of obviousness has not been established. In view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

VII. Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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